

The following is a complete listing of all claims in the application, with an indication of the status of each:

Listing of claims:

We claim:

1. (Original) A computer-assisted method for creating and displaying a model of a molecule in which the residues of said molecule that are affected by binding of a ligand to said molecule are highlighted using a programmed computer including a processor , an input device, and an output device, comprising,
inputting into said programmed computer, through the input device, data including an identity and three-dimensional coordinates of said molecule,
generating, using the processor, a conformational ensemble for said molecule, wherein said conformational ensemble is comprised of a number of conformational states of said molecule sufficient to achieve convergence to a stable ensemble average,
determining, using the processor, a predicted Gibbs energy for each of said conformational states,
identifying, using the processor, binding competent conformational states,
modifying said predicted Gibbs energy for said binding competent conformational states to form a modified Gibbs energy using an equation

$$\Delta G_i = \Delta G_i^0 - RT \ln \frac{(1 + K_{a,i} [X])}{(1 + K_{a,0} [X])}$$

wherein ΔG_i is said modified Gibbs energy, ΔG_i^0 is said predicted Gibbs energy, R is a gas constant, T is an absolute temperature, $K_{a,0}$ is a binding constant to a reference state, $K_{a,i}$ is a binding constant to a given binding competent conformational state, and [X] is a concentration of said ligand,

forming, using said processor, a first and second set of Gibbs energy values, wherein said first set of Gibbs energy values represents Gibbs energy values in the presence of said ligand and said second set of Gibbs energy values represents Gibbs energy values in the absence of said ligand,

28 computing, using the processor, a first set of probabilities from said first set of Gibbs
29 energy values and a second set second of probabilities from said second set of Gibbs energy
30 values, wherein said first set of probabilities represents probability values in the presence of said
31 ligand and said second set of probabilities represents probability values in the absence of said
32 ligand,

33 calculating, using the processor, a first set of residue stability constants in the presence of
34 ligand from said first set of probabilities and a second set of residue stability constants in the
35 absence of ligand from said second set of probabilities,

36 comparing, using the processor, said first and second sets of residue stability constants,
37 selecting affected residues of said molecule, wherein said affected residues exhibit a
38 difference in stability constant in said first and said second set of stability constants,

39 creating, using the processor, a model of said molecule wherein said affected residues are
40 highlighted, and

41 displaying, using the output device, said model of said molecule wherein said affected
42 residues are highlighted.

1 Claim 2 (Original). The method of claim 1 wherein said step of identifying binding competent
2 conformational states comprises the steps of

3 ascertaining a contribution of each residue of said conformational states in said ensemble
4 to the Gibbs energy of binding for said ligand,

5 defining binding determinant residues, wherein said binding determinant residues
6 contribute in excess of about 100 cal/mole to the Gibbs energy of binding, and

7 establishing as binding competent conformational states those conformational states in
8 which said binding determinant residues are in a native conformation.

1 Claim 3 (Original). The method of claim 1 wherein said molecule is a protein.

1 Claim 4 (Original). A computer program product comprising a computer-readable medium
2 having stored thereon a computer program including instructions for causing a computer to:

3 receive data including an identity and three-dimensional coordinates of a molecule,

4 generate a conformational ensemble for said molecule, wherein said conformational
5 ensemble is comprised of a plurality of conformational states of said molecule,
6 determine a predicted Gibbs energy for each of said plurality of states in said
7 conformational ensemble,
8 identify binding competent conformational states,
9 modify said predicted Gibbs energy for said binding competent conformational states to
10 form a modified Gibbs energy using an equation

$$\Delta G_i = \Delta G_i^0 - RT \ln \frac{(1 + K_{a,i} [X])}{(1 + K_{a,0} [X])}$$

16 wherein ΔG_i is said modified Gibbs energy, ΔG_i^0 is said predicted Gibbs energy, R is a
17 gas constant, T is an absolute temperature, $K_{a,0}$ is a binding constant to a reference state, $K_{a,i}$ is a
18 binding constant to a given binding competent conformational state, and $[X]$ is a concentration of
19 said ligand,

20 compute a first set of probabilities from said first set of Gibbs energy values and a
21 second set of probabilities from said second set of Gibbs energy values, wherein said first
22 set of probabilities represents probability values in the presence of said ligand and said second set
23 of probabilities represents probability values in the absence of said ligand,

24 calculate a first set of residue stability constants in the presence of ligand from said first
25 set of probabilities and a second set of residue stability constants in the absence of ligand from
26 said second set of probabilities,

27 compare said first and second sets of residue stability constants,
28 select affected residues of said molecule, wherein said affected residues exhibit a
29 difference in stability constant in said first and said second set of stability constants,
30 create a model of said molecule wherein said affected residues are highlighted., and
31 display said model of said molecule.